

Figure 1

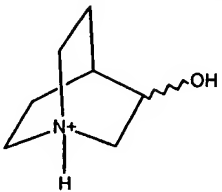
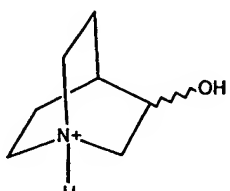
<u>Allosteric Effector</u>	<u>Structure or Name</u>
ICP6	Nona-cyclohexylammonium tri-sodium inositol hexaphosphate
IC2P1	Bis-dicyclohexylammonium deca-sodium inositol hexaphosphate
IC2P2	Octa-dicyclohexylammonium inositol hexaphosphate
SV42	Hexa-dibenzylmethylammonium inositol hexaphosphate
SV44	 <p>Hepta inositol hexaphosphate</p>
SV45	 <p>Dodeca- inositol hexaphosphate</p>
SV46	Nona-piperidinium inositol hexaphosphate

Figure 2

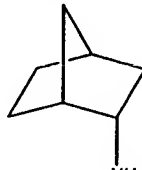
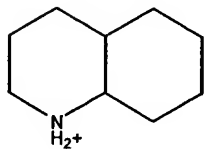
<u>Allosteric Effector</u>	<u>Structure or Name</u>
SV47	Penta-H ₃ N-Phe-OMe inositol hexaphosphate
SV48	Nona-H ₃ N-Phe-OMe inositol hexaphosphate
SV51	Hexa-1-indanylammonium inositol hexaphosphate
SV52	 Hepta- NH₃⁺ inositol hexaphosphate
SV53	 Nona- NH₂⁺ inositol hexaphosphate
SV55	Hepta-H ₃ N-Phe-OEt inositol hexaphosphate
SV56	Hexa-H ₃ N-Phe-OEt inositol hexaphosphate
SV57	Octa-H ₃ N- <i>sec</i> -Leu-Ot-Bu inositol hexaphosphate
SV58	Dodeca-diisopropylammonium inositol hexaphosphate
SV59	Octa-H ₂ N-Pro-Ot-Bu inositol hexaphosphate

Figure 3

<u>Allosteric Effector</u>	<u>Structure or Name</u>
SV68	Deca-H ₃ N-Tyr-OEt inositol hexaphosphate
SV71	Undeca-4-t-butylcyclohexylammonium inositol hexaphosphate
SV73	Tetra-cyclohexyl-1,2-bis-ammonium inositol hexaphosphate
SV74	Undeca-adamantylammonium inositol hexaphosphate
SV75	Nona-cycloheptylammonium inositol hexaphosphate
SV78	Undeca-cyclopentylammonium inositol hexaphosphate
SV80	Hepta-H ₃ N-Try-OEt inositol hexaphosphate
SV81	Undeca-cyclohexylammonium inositol hexaphosphate
SV99	Hexa-dimethylcyclohexylammonium inositol hexaphosphate
SV115	Nona-hexylammonium inositol hexaphosphate
SV131	Undeca-cyclooctanylammonium inositol hexaphosphate
SV135	Nona-octylammonium inositol hexaphosphate
IP12	Hepta-tributylammonium inositol hexaphosphate

Figure 4

Cyclic Primary Amines

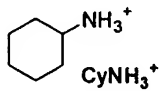
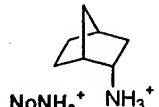
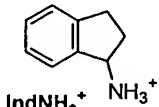
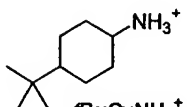
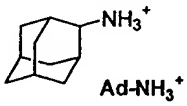
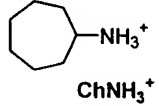
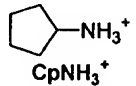
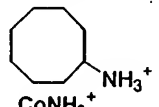

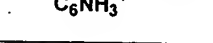

Reference	Counter-cation	Number	Mol. Formula	Mol. Weight (g.mol ⁻¹)
ICP ₁		1 Bu ₃ NH ⁺		
		6 CyNH ₃ ⁺ 5 Na ⁺	C ₅₄ H ₁₁₈ O ₂₄ N ₇ P ₆ Na ₅	1550.37
ICP ₂		9 CyNH ₃ ⁺ 3 Na ⁺	C ₆₀ H ₁₃₀ O ₂₄ N ₉ P ₆ Na ₃	1616.57
ICP ₃		9 CyNH ₃ ⁺ 3 Na ⁺	C ₆₀ H ₁₃₀ O ₂₄ N ₉ P ₆ Na ₃	1616.57
ICP ₄		11 CyNH ₃ ⁺ 1 Na ⁺	C ₇₂ H ₁₆₀ O ₂₄ N ₁₁ P ₆ Na ₁	1772.97
ICP ₅		9 CyNH ₃ ⁺ 3 Na ⁺	C ₆₀ H ₁₃₀ O ₂₄ N ₉ P ₆ Na ₃	1616.57
ICP ₆		9 CyNH ₃ ⁺ 3 Na ⁺	C ₆₀ H ₁₃₀ O ₂₄ N ₉ P ₆ Na ₃	1616.57
SV52		7 No-NH ₃ ⁺	C ₅₅ H ₁₀₄ O ₂₄ N ₇ P ₆	1433.32
SV51		6 Ind-NH ₃ ⁺	C ₆₀ H ₈₄ O ₂₄ N ₆ P ₆	1459.21
				H _{5.80} N _{5.76} C _{49.39}
SV69		11 <i>t</i> BuCy-NH ₃ ⁺	C ₁₁₆ H ₂₄₉ O ₂₄ N ₁₁ P ₆	2368.18
SV71		7 <i>t</i> BuCy-NH ₃ ⁺	C ₇₆ H ₁₆₅ O ₄₀ N ₈ P ₆	1747.03
				H _{9.52} C _{52.26} N _{5.61}
SV74		11 Ad-NH ₃ ⁺	C ₁₁₆ H ₁₉₄ O ₂₄ N ₁₁ P ₆	2312.74
				H _{8.46} C _{60.24} N _{6.66}
SV75		9 Ch-NH ₃ ⁺	C ₆₉ H ₁₅₃ O ₂₄ N ₉ P ₆	1819.52
				H _{5.98} C _{47.53} N _{4.62}
SV76		11 Cp-NH ₃ ⁺	C ₆₁ H ₁₃₉ O ₂₄ N ₁₁ P ₆	1596.69
				H _{8.77} C _{45.89} N _{9.65}
SV131		11 Co-NH ₃ ⁺	C ₉₄ H ₂₀₅ O ₂₄ N ₁₁ P ₆	2059.58
SV220		10 Co-NH ₃ ⁺	C ₈₆ H ₁₈₈ O ₂₄ N ₁₀ P ₆	1932.35

Figure 5

Acyclic Primary Amines

SV112		7 C ₆ NH ₃ ⁺	C ₄₈ H ₁₂₃ O ₂₄ N ₇ P ₆	1368.39
SV115		9 C ₆ NH ₃ ⁺	C ₆₀ H ₁₅₃ O ₂₄ N ₉ P ₆	1570.78
SV135		9 C ₈ NH ₃ ⁺	C ₇₈ H ₁₈₉ O ₂₄ N ₉ P ₆	1821

Amino-acids

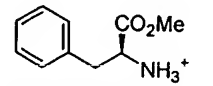
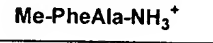
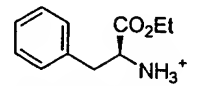

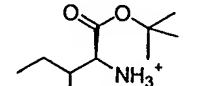
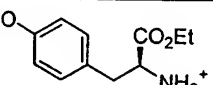
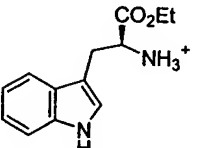
SV47		5 Me-PheAla-NH ₃ ⁺	C ₅₆ H ₇₆ O ₃₄ N ₅ P ₆	1549.08
SV48		9 Me-PheAla-NH ₃ ⁺	C ₉₆ H ₁₃₂ O ₄₂ N ₉ P ₆	2270.00
SV55		7 Et-PheAla-NH ₃ ⁺	C ₈₃ H ₁₂₃ O ₃₈ N ₇ P ₆	2012.77
SV56		6 Et-PheAla-NH ₃ ⁺	C ₇₂ H ₁₀₈ O ₃₆ N ₆ P ₆	H _{6.16} N _{4.87} C _{49..53} 1819.52
SV57		8 tBu-iLeu-NH ₃ ⁺	C ₇₈ H ₁₅₄ O ₄₀ N ₈ P ₆	H _{5.98} C _{47.53} N _{4.62} 1819.52
SV68		10 Et-Tyr-NH ₃ ⁺	C ₁₁₆ H ₁₆₈ O ₅₄ N ₁₀ P ₆	2752.51
SV80		7 Et-Try-NH ₃ ⁺	C ₉₇ H ₁₃₀ O ₃₈ N ₁₄ P ₆	H _{6.15} C _{50.62} N _{5.09} 2286.03

Figure 6

Secondary Amines

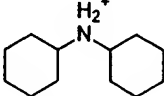
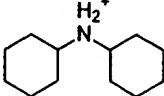

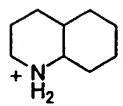
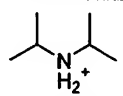
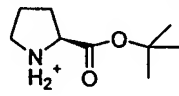
Reference	Counter-cation	Number	Mol. Formula	Mol. Weight (g.mol ⁻¹)
IC2P ₁		2 Cy ₂ NH ₃ ⁺ 10 Na ⁺	C ₃₀ H ₅₄ O ₂₄ N ₂ P ₆ Na ₁₀	1242.50
IC2P ₂	 Cy ₂ NH ₂ ⁺	8 Cy ₂ NH ₃ ⁺	C ₁₀₂ H ₂₀₂ O ₂₄ N ₈ P ₆	2110.63
SV46	PinH ₂ ⁺ 	9 PinH ₂ ⁺	C ₅₁ H ₁₁₇ O ₂₄ N ₉ P ₆	1426.39
SV53	 DHQ-NH ₂ ⁺	9 PinH ₂ ⁺	C ₈₇ H ₁₇₁ O ₂₄ N ₉ P ₆	1913.22 H _{9.01} C _{54.62} N _{6.59}
SV58	 iPr ₂ -NH ₂ ⁺	12 iPr ₂ NH ₂ ⁺	C ₇₈ H ₁₉₈ O ₂₄ N ₁₂ P ₆	1874.36 H _{10.65} C _{49.98} N _{8.97}
SV59	 tBu-Pro-NH ₂ ⁺	8 tBu-ProNH ₂ ⁺	C ₇₈ H ₁₅₄ O ₄₀ N ₈ P ₆	1874.36 H _{7.65} C _{46.15} N _{5.52}

Figure 7

Tertiary Amines

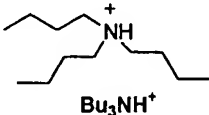
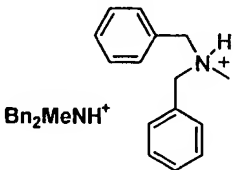
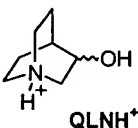
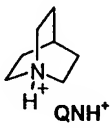
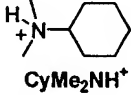
Reference	Counter-cation	Number	Mol. Formula	Mol. Weight (g.mol ⁻¹)
IP ₁₂	 Bu ₃ NH ⁺	7 Bu ₃ NH ⁺ 5 Na ⁺	C ₉₀ H ₂₀₂ O ₂₄ N ₇ P ₆ Na ₆	2067.43
SV42	 Bn ₂ MeNH ⁺	6 Bn ₂ MeNH ⁺	C ₉₆ H ₁₂₀ O ₂₄ N ₆ P ₆	1550.66 H _{6.27} C _{59.81} N _{4.36}
SV44	 QLNH ⁺	7 QLNH ⁺	C ₅₅ H ₁₀₉ O ₃₁ N ₇ P ₆	1550.35
SV45	 QNH ⁺	12 QNH ⁺	C ₉₀ H ₁₇₄ O ₂₄ N ₁₂ P ₆	1994.30 H _{8.79} C _{54.2} N _{8.43}
SV99	 CyMe ₂ NH ⁺	6 CyMe ₂ NH ⁺	C ₅₄ H ₁₁₄ O ₂₄ N ₆ P ₆	1417.38 H _{8.11} C _{45.76} N _{5.93}

Figure 8

Diamines

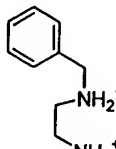
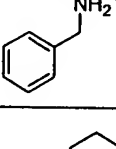
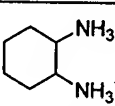
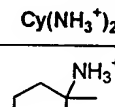
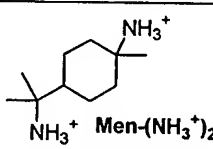
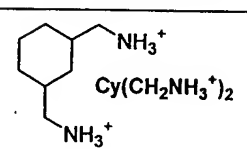
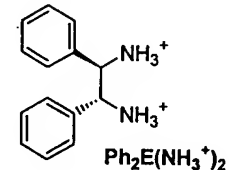
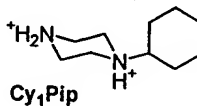
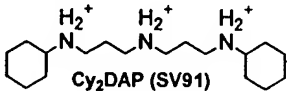
Reference	Counter-cation	Number	Mol. Formula	Mol. Weight (g.mol ⁻¹)
SV72	 Bn ₂ E(NH ₂ ⁺) ₂	5 Bn ₂ E(NH ⁺) ₂	C ₈₆ H ₁₀₈ O ₂₄ N ₁₀ P ₆	1851.71 H _{5.88} C _{55.78} N _{7.56}
SV76	 Bn ₂ E(NH ₂ ⁺) ₂	4 Bn ₂ E(NH ⁺) ₂	C ₇₀ H ₈₈ O ₂₄ N ₈ P ₆	1611.36 H _{5.5} C _{52.18} N _{6.95}
SV73	 Cy(NH ₃ ⁺) ₂	4 Cy(NH ₃ ⁺) ₂	C ₃₀ H ₆₈ O ₂₄ N ₈ P ₆	1110.76
SV92	 Cy(NH ₃ ⁺) ₂	5 Cy(NH ₃ ⁺) ₂	C ₃₆ H ₈₈ O ₂₄ N ₁₀ P ₆	1231.00
SV89	 Men-(NH ₃ ⁺) ₂	8 Men-(NH ₃ ⁺) ₂	C ₈₆ H ₂₂₈ O ₂₄ N ₁₆ P ₆	2056.71
SV94	 Cy(CH ₂ NH ₃ ⁺) ₂	5 Cy-(CH ₂ NH ₃ ⁺) ₂	C ₄₆ H ₁₀₈ O ₂₄ N ₁₀ P ₆	1371.27
SV95	 Ph ₂ E(NH ₃ ⁺) ₂	5 Ph ₂ E(NH ₃ ⁺) ₂	C ₇₆ H ₉₈ O ₂₄ N ₁₀ P ₆	1721.52
SV97	 Cy ₁ Pip	9 Cy ₁ Pip	C ₉₆ H ₁₉₂ O ₂₄ N ₁₀ P ₆	2056.50

Figure 9

Triamines

Reference	Counter-cation	Number	Mol. Formula	Mol. Weight (g.mol ⁻¹)
SV101	 Cy ₂ DAP (SV91)	2 Cy ₂ DAP	C ₄₂ H ₉₂ O ₂₄ N ₆ P ₆	1251.07
SV120		3.6 Cy ₂ DAP	C ₇₁ H ₁₄₅ O ₂₄ N ₁₁ P ₆	1722.85

Tetra-amines

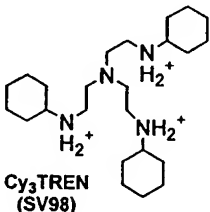
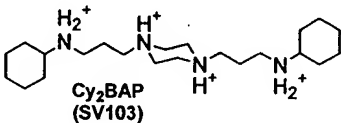
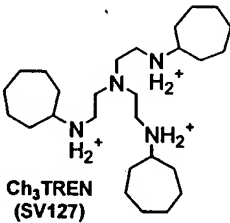
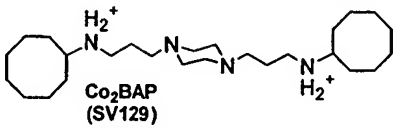
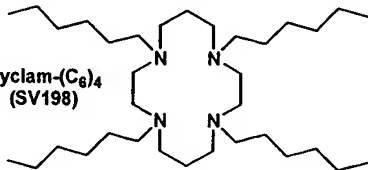
Ref	Counter-cation	Number	Mol. Formula	Mol. Weight (g.mol ⁻¹)
SV102	 Cy ₃ TREN (SV98)	3 Cy ₃ TREN	C ₇₈ H ₁₆₂ O ₂₄ N ₁₂ P ₆	1838.07
SV106	 Cy ₂ BAP (SV103)	4 Cy ₂ BAP	C ₉₄ H ₁₉₄ O ₂₄ N ₁₆ P ₆	2118.53
SV137	 Ch ₃ TREN (SV127)	2 Ch ₃ TREN	C ₆₀ H ₁₂₀ O ₂₄ N ₈ P ₆	1523.51
SV141	 Co ₂ BAP (SV129)	3 Co ₂ BAP	C ₈₄ H ₁₇₄ O ₂₄ N ₁₂ P ₆	1922.2
SV202	 Cyclam-(C ₆) ₄ (SV198)	2 Cyclam-(C ₆) ₄	C ₇₄ H ₁₆₂ O ₂₄ N ₈ P ₆	1733.99

Figure 10

Hexa-amines

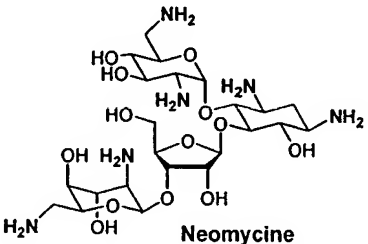
Ref	Counter-cation	Number	Mol. Formula	Mol. Weight (g.mol ⁻¹)
SV216	 <p>Neomycine</p>	1 Neomycin/IHP	C ₂₉ H ₆₄ O ₃₇ N ₆ P ₆	1274.69
SV217		2 Neomycin/IHP	C ₅₂ H ₁₁₀ O ₅₀ N ₁₂ P ₆	1889.35

Figure 11 Partition coefficients of IHP ammonium salts (at 30 mM).

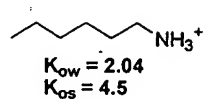
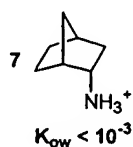
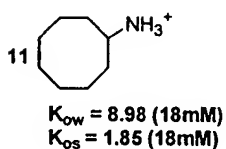
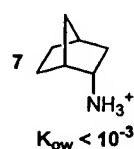
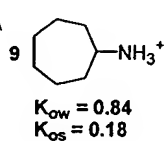
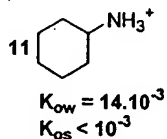
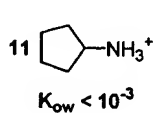
Primary amines

aliphatic amines

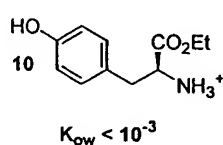
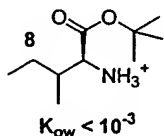
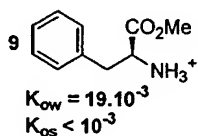
refers to the number of ammoniums associated to IHP

K_{ow} = octanol/water partition coefficient

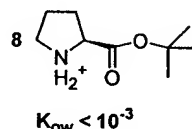
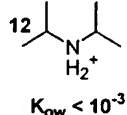
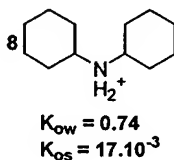
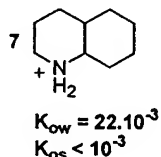
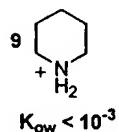
K_{os} = octanol/serum partition coefficient



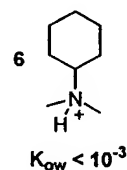
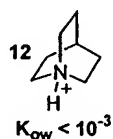
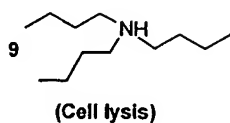
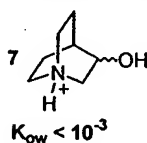
amino esters



Secondary amines



Tertiary amines



Water solubility < 1mM

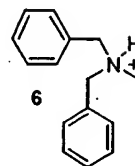
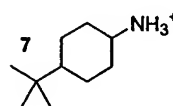
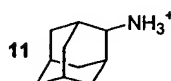
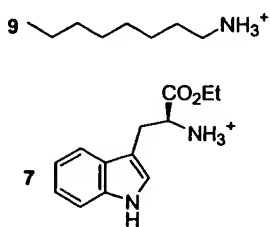
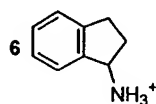
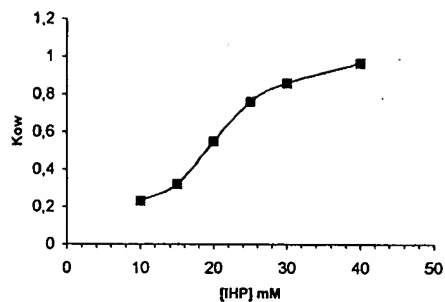
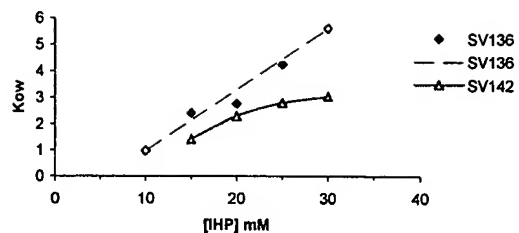


Figure 12



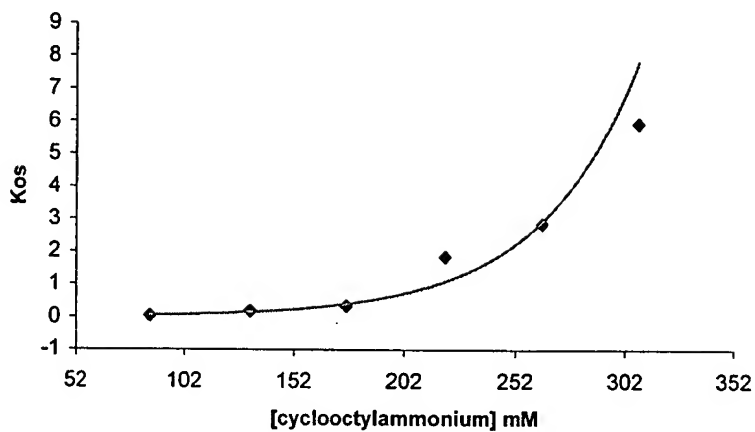
Experiments SV136 and SV142.

Compound SV131 (IHP, 11 cyclooctylammonium) was dissolved in 1-octanol at various concentrations and agitated with an equal volume of artificial serum (SV136) or human serum (SV142).

Experiment SV134.

Compound SV75 (IHP, 9 cycloheptylammonium) was dissolved in octanol at various concentrations and agitated with an equal volume of water.

Figure 13



IHP uptake in 1-octanol by cyclooctylammonium ions. IHP, dodecasodium form, was dissolved in human serum ([IHP] = 22 mM, pH = 7.4). Each samples were agitated 2 days with an equal volume of octanolic solution of cyclooctylamine,HCl at different concentrations. Partition coefficients K_{0s} were measured by ^{31}P -NMR.

Figure 14 P₅₀ values obtained from O₂-dissociation curves using whole blood.

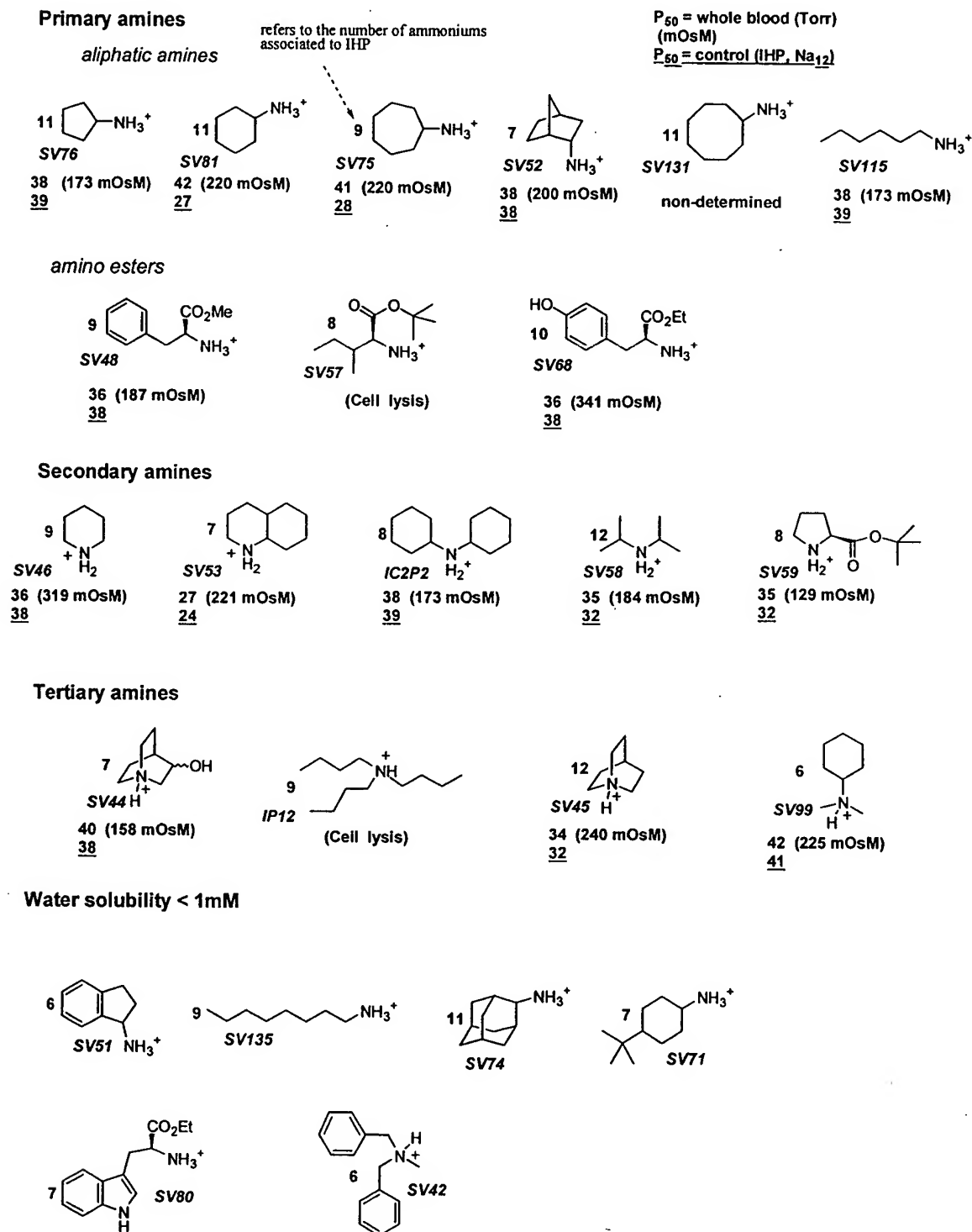


Figure 15

Effector	P50 CONTROL WB mmHg	P50 EFF: WB mmHg	CONC. EFF mM	CONC EFF:WB mM	OSMOL. EFF mOsM	pH EFF.	pH EFF:WB or EFF:/Hb	Volume Ratio EFF:WB
HBS+					310		7.22	
/Hb HBS+ in							7.22	
ICP6								
WB	27.5	39	30	22	220		7.23	1:0.375
WB	27.5	27.5	30	22	312		7.2	1:0.375
WB	27.5	31	30	22	262		7.21	1:0.375
WB	27.5	27.5	60	44	318		7.32	1:1.5
/Hb	16	43.5					7.18	0.25 μ M EFF
IC2P1								
WB	38.5	39.5	30	22	160		6.04	1:0.375
WB	38.5	39.5	30	22	160		6.03	1:0.375

/Hb = free hemoglobin; WB = whole blood; EFF = effector.

Figure 16

Effector	P50 CONTROL WB mmHg	P50 EFF: WB mmHg	CONC. EFF mM	CONC EFF:WB mM	OSMOL. EFF mOsM	pH EFF.	pH EFF:WB or EFF: <i>f</i> Hb	Volume Ratio EFF:WB
IC2P2								
WB	38	41	30	22	302	7.44	6.94	1:0.375
WB	38	39.5	30	22	323		7.21	1:0.375
<i>f</i> Hb	16.5	41.5					7.17	0.25 μ M EFF
SV44								
WB	37.5	40	30	22	158		7.23	1:0.375
WB	37.5	37.5	30	12	315		6.98	1:1.5
<i>f</i> Hb	16	42.5					7.17	0.25 μ M EFF
SV46								
WB	38.5	36	30	12	319		7.13	1:1.5
<i>f</i> Hb	16	42						0.25 μ M EFF
SV47								
WB	38.5	38.5	30	22	173		6.93	1:0.375
WB	38.5	38.5	30	12	338		7.41	1:1.5
<i>f</i> Hb	16	45.5					7.11	0.25 μ M EFF
SV48								
WB	38.5	36	30	22	187		6.88	1:0.375
WB	38.5	37	30	12	326		7.26	1:1.5
<i>f</i> Hb	16	48					7.1	0.25 μ M EFF
SV51								
WB	25	28.5	30	22	220	7.67	7.36	1:0.375
WB	25	24.5	30	12	220	7.67		1:1.5
WB	24.5	27	30	12	220	7.51	6.99	1:1.5
WB	28.5	28.5	30	12	344	7.64	7.27	1:1.5
<i>f</i> Hb	16	44					7.19	0.25 μ M EFF
SV52								
WB	38.5	38.5	30	22	200		6.4	1:0.375
<i>f</i> Hb	16	45.5					7.15	0.25 μ M EFF
SV53								
WB	24.5	27	30	12	221	7.12	6.6	1:1.5
WB	28.5	28.5	30	12	362	7.86	7.27	1:1.5
<i>f</i> Hb	16	43					7.18	0.25 μ M EFF

*f*Hb = free hemoglobin; WB = whole blood; EFF = effector

Figure 17

Effector	P50 CONTROL WB mmHg	P50 EFF: WB mmHg	CONC. EFF mM	CONC EFF:WB mM	OSMOL. EFF mOsm	pH EFF.	pH EFF:WB or EFF:/fHb	Volume Ratio EFF:WB
SV55								
WB	28.5	28.5	30	12	346	7.58	7.21	1:1.5
fHb	16	48.5					7.15	0.25 μ M EFF
SV56								
WB	28.5	28.5	30	12	325	7.35	7.36	1:1.5
fHb	16	41					7.15	0.25 μ M EFF
SV45								
WB	32.5	34.5	30	22	240	7.38		1:0.375
fHb	16.5	45.5					7.18	0.25 μ M EFF
SV57								
WB	32.5	Lysis	30	22	323	7.28		1:0.375
fHb	16.5	43					7.16	0.25 μ M EFF
SV58								
WB	32.5	35.6	30	22	184	7.41		1:0.375
fHb	16.5	43					7.17	0.25 μ M EFF
SV59								
WB	32.5	35.3	30	22	129	7.32		1:0.375
fHb	16.5	41.5					7.16	0.25 μ M EFF
SV68								
WB	38	36	30	12	341		7.38	1:1.5
fHb	16.5	50					7.15	0.25 μ M EFF
SV73								
WB	38	36	30	12	72		6.17	1:1.5
WB	38	36	30	12	335		7.31	1:1.5
WB	38	57	30	22	68		7.54	1:0.375
fHb	16.5	43					7.2	0.25 μ M EFF
SV75								
fHb	16.5	45					7.2	0.25 μ M EFF
SV78								
WB	38	36	30	12	309		7.3	1:1.5
fHb	16.5	46					7.2	0.25 μ M EFF
SV81								
WB	38	36	30	12	341		7.38	1:1.5
fHb	16.5	44					7.2	0.25 μ M EFF

fHb = free hemoglobin; WB = whole blood; EFF = effector.

Figure 18

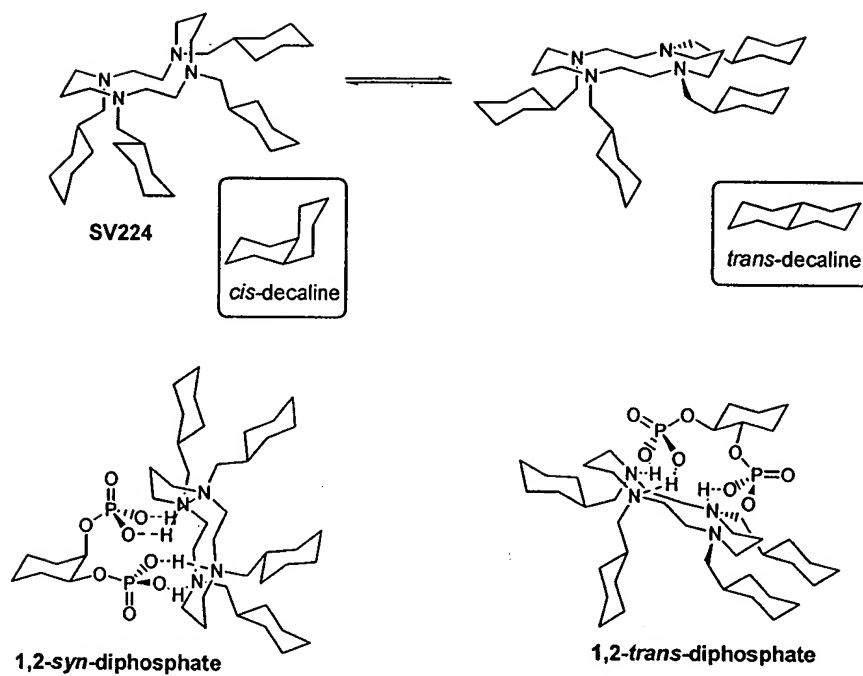
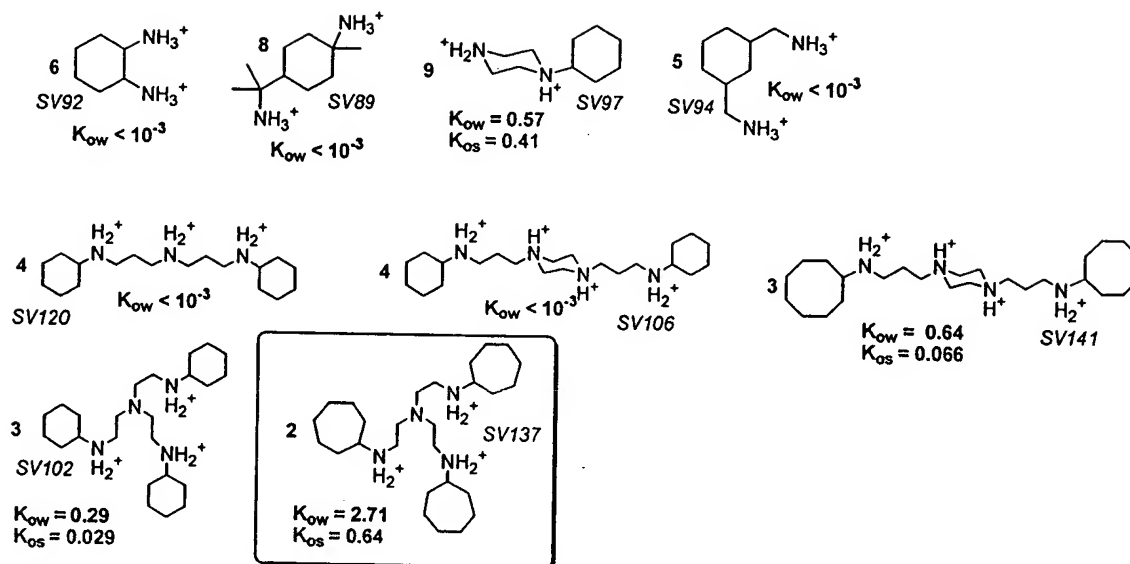


Figure 19

K_{ow} = octanol/water partition coefficient
 K_{os} = octanol/serum partition coefficient

Polyamines



Water solubility < 1mM

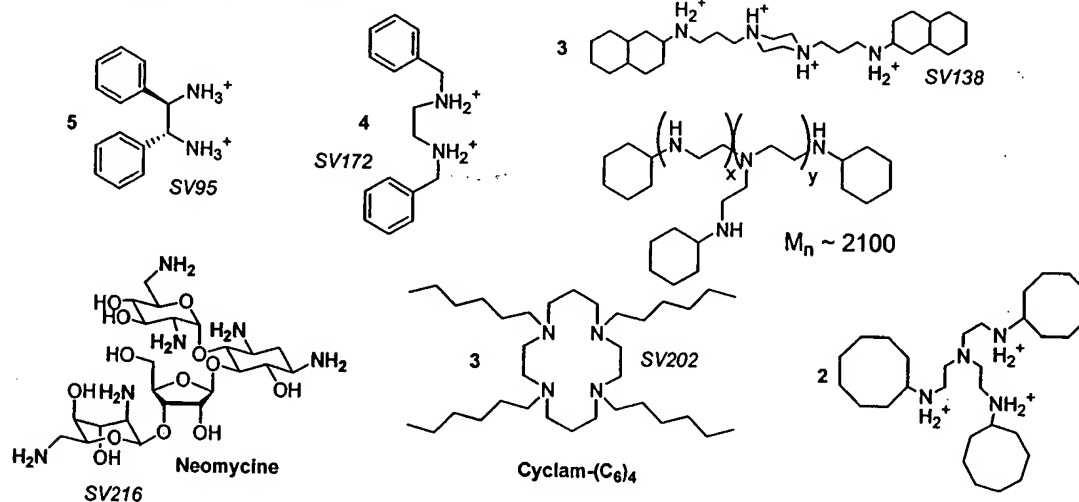


Figure 20

